

AMENDMENTS TO THE CLAIMS

1. (currently amended) A 38-residue or 39-residue CRFR1 ligand cyclic peptide which binds to CRFR1 with an affinity substantially greater than it binds to CRFR2, which peptide has the following formula, or a nontoxic salt thereof:
$$Y_1\text{-Pro-Pro-R}_6\text{-Ser-R}_8\text{-Asp-R}_{10}\text{-R}_{11}\text{-D-Phe-R}_{13}\text{-R}_{14}\text{-R}_{15}\text{-Arg-R}_{17}\text{-R}_{18}\text{-R}_{19}\text{-R}_{20}\text{-R}_{21}\text{-R}_{22}\text{-R}_{23}\text{-R}_{24}\text{-R}_{25}\text{-R}_{26}\text{-R}_{27}\text{-R}_{28}\text{-R}_{29}\text{-Gln-Glu-R}_{32}\text{-R}_{33}\text{-R}_{34}\text{-Arg-R}_{36}\text{-R}_{37}\text{-R}_{38}\text{-R}_{39}\text{-R}_{40}\text{-R}_{41}\text{-NH}_2$$
 wherein Y_1 is an acyl group having not more than 15 carbon atoms or is radioiodinated tyrosine; R_6 is Ile, Met or Nle; R_8 is Leu or Ile; R_{10} is Leu or CML; R_{11} is Thr or Ser; R_{13} is His, Tyr or Glu; R_{14} is CML or Leu; R_{15} is CML or Leu; R_{17} is Glu, CML, Asn or Lys; R_{18} is Val, CML, Nle or Met; R_{19} is CML, Leu or Ile; R_{20} is Glu, D-Glu or His; R_{21} is Nle, Leu, CML or Met; R_{22} is Ala, D-Ala, Aib, Thr, Asp or Glu; R_{23} is Arg or Lys; R_{24} is Ala, Gln, Ile, Asn, CML or Aib; R_{25} is Asp or Glu; R_{26} is Gln, Asn or Lys; R_{27} is CML, Glu, Gln or Leu; R_{28} is Ala, Lys, Arg or Aib; R_{29} is Gln, Aib or Glu; R_{32} is Aib or an L- or D-isomer of a natural α -amino acid other than Cys; R_{33} is Aib or an L- or D-isomer of Ser, Asn, Leu, Ala, CML or Ile; R_{34} is Lys or Orn; R_{36} is Lys, Orn, Arg, Har, CML or Leu; R_{37} is CML, Leu, Nle or Tyr; R_{38} is Nle, Met, CML or Leu; R_{39} is Glu, Aib or Asp; R_{40} is Ile, Aib, CML, Thr, Glu, Ala, Val, Leu, Nle, Phe, Nva, Gly or Gln; and R_{41} is Ala, Aib, Ile, CML, Gly, Val, Leu, Nle, Phe, Nva or Gln; provided that a cyclizing bond ~~may exist~~ exists between Glu in position 31 and R_{34} and provided further that ~~D-2Nal~~ D- β -(2-naphthyl)alanine(D-2Nal) or D-Leu may be substituted for D-Phe.

2. (currently amended) A peptide according to claim 1 having the formula: (cyclo 31-34) $Y_1\text{-Pro-Pro-R}_6\text{-Ser-R}_8\text{-Asp-Leu-R}_{11}\text{-D-Phe-His-R}_{14}\text{-Leu-Arg-Glu-R}_{18}\text{-Leu-R}_{20}\text{-Nle-R}_{22}\text{-R}_{23}\text{-Ala-R}_{25}\text{-Gln-Leu-Ala-R}_{29}\text{-Gln-Glu-R}_{32}\text{-R}_{33}\text{-R}_{34}\text{-Arg-R}_{36}\text{-R}_{37}\text{-Nle-R}_{39}\text{-R}_{40}\text{-R}_{41}\text{-NH}_2$ wherein Y_1 is an acyl group having not more than 7 carbon atoms; R_{20} is Glu or D-Glu; R_{22} is Ala or Thr; R_{29} is Gln or Glu; R_{32} is His, Aib, Ala, Gly, Leu, Gln or Glu; R_{36} is Lys or Leu; R_{37} is Leu or CML; R_{39} is Glu or Asp; R_{40} is Ile, CML or Glu; and R_{41} is Ile, Aib or Ala; with the remaining variables being as defined in claim ~~2~~ 1.

3. (original) A peptide according to claim 1 having the formula:
(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-
Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-Leu-Ala-Gln-Gln-Glu-His-Ser-Lys-Arg-Lys-Leu-
Nle-Glu-Ile-Ile-NH₂, or
(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-
Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-CML-Ala-Gln-Gln-Glu-His-Ser-Lys-Arg-Lys- Leu-
Nle-Glu-Ile-CML-NH₂; or
(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-
Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-CML-Ala-Gln-Gln-Glu-His-Aib-Lys-Arg-Lys- Leu-
Nle-Glu-Ile-CML-NH₂.

4. (canceled)

5. (currently amended) A CRF cyclic peptide according to claim 1 having the formula:
Y₁-Pro-Pro-R₆-Ser-R₈-Asp-Leu-R₁₁-D-Phe-His-R₁₄-Leu-Arg-Glu-R₁₈-Leu-R₂₀-Nle-R₂₂-
R₂₃-Ala-R₂₅-Gln-Leu-Ala-R₂₉-Gln-Glu-R₃₂-R₃₃-R₃₄-Arg-R₃₆-R₃₇-Nle-R₃₉-R₄₀-R₄₁-NH₂
wherein Y₁ is an acyl group having not more than 7 carbon atoms; R₂₀ is Glu or D-Glu;
R₂₂ is Ala or Thr; R₂₃ is Arg or Lys; R₂₉ is Gln or Glu; R₃₂ is His, D-His, Aib or Ala; R₃₆
is Lys or Leu; R₃₇ is Leu or CML; R₃₉ is Glu or Asp; R₄₀ is Ile, CML or Glu; and R₄₁ is
Ile, Aib or Ala; wherein the remaining variables are as defined in claim 1 ~~2 and wherein~~
~~the side chains of Glu³¹ and R₃₄ may be covalently connected.~~

6. (original) A peptide according to claim 1 wherein R₁₈ is Val, R₂₂ is Ala,
R₂₃ is Arg, R₂₄ is Ala, R₂₅ is Glu, R₂₈ is Ala, R₃₉ is Glu, and R₄₁ is Ile.

7. (original) A peptide according to claim 1 having the following formula, or
a nontoxic salt thereof:

(cyclo 31-34)Y₁-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-R₂₂-R₂₃-Ala-Glu-Gln-R₂₇-Ala-Gln-Gln-Glu-R₃₂-R₃₃-Lys-Arg-Lys-Leu-Nle-Glu-R₄₀-Ile-NH₂ wherein R₂₂ is Ala or Thr; R₂₇ is Leu or CML; R₃₂ is His or Aib; R₃₃ is Ser or Aib; and R₄₀ is Ile or CML.

8. (canceled)

9. (currently amended) A peptide according to claim 1 which is useful as a tracer that selectively ~~bonds~~ binds to CRFR1 wherein \forall Y₁ is radioiodinated D-Tyr or L-Tyr.

10. (canceled)

11. (new) A peptide according to claim 1 having the formula:

(cyclo 31-34) Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle- Thr-Lys-Ala-Asp-Gln-Leu-Ala-Gln-Gln-Glu-His-Ser-Lys-Arg-Lys-Leu-Nle-Asp-Ile- Ala-NH₂; or

(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-CML-Ala-Gln-Gln-Glu-His-Ser-Lys-Arg-Lys- Leu-Nle-Glu-Ile-Ile-NH₂; or

(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-Leu-Ala-Gln-Gln-Glu-His-Aib-Lys-Arg-Lys- Leu-Nle-Glu-Ile-Ile-NH₂.

12. (new) A peptide according to claim 1 having the formula:

(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-CML-Arg-Glu-Val-CML-Glu-Nle-Ala-Arg-Ala-Glu-Gln-Leu-Ala-Gln-Gln-Glu-His-Ser-Lys-Arg-Lys-Leu-Nle-Glu-Ile-Ile-NH₂, or

(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-CML-Leu-Arg-Glu-Val-Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-Leu-Ala-Gln-Gln-Glu-His-Ser-Lys-Arg-Lys-Leu-Nle-Glu-Ile-Ile-NH₂; or
(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-CML-Ala-Gln-Gln-Glu-His-D-Ser-Lys-Arg-Lys-Leu-Nle-Glu-CML-Ile-NH₂.

13. (new) A 38-residue or 39-residue CRF agonist cyclic peptide, or a nontoxic salt thereof, which binds to CRFR1 with an affinity substantially greater than it binds to CRFR2, which peptide has the following formula:

Y₁-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-R₁₄-R₁₅-Arg-R₁₇-R₁₈-R₁₉-Glu-Nle-Ala-Arg-Ala-Glu-Gln-R₂₇-Ala-Gln-Gln-Glu-R₃₂-R₃₃-Lys-Arg-R₃₆-R₃₇-Nle-Glu-R₄₀-R₄₁-NH₂ wherein Y₁ is an acyl group having not more than 15 carbon atoms or is radioiodinated tyrosine; R₁₄ is CML or Leu; R₁₅ is CML or Leu; R₁₇ is Glu or CML; R₁₈ is Val or CML; R₁₉ is CML or Leu; R₂₇ is CML or Leu; R₃₂ is Aib, His or D-His; R₃₃ is Aib, D-Ala, D-Ser or Ser; R₃₆ is Lys or CML; R₃₇ is CML or Leu; R₄₀ is Ile or CML; and R₄₁ is Ile or CML; provided that a cyclizing bond exists between Glu in position 31 and Lys in position 34 and provided further that D-β-(2-naphthyl)alanine(D-2Nal) or D-Leu may be substituted for D-Phe.

14. (new) A CRF agonist peptide, or a nontoxic salt thereof, which binds to CRFR1 with an affinity substantially greater than it binds to CRFR2, which peptide has the following formula:

(cyclo 31-34) Y₁-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-Leu-Ala-Gln-Gln-Glu-His-Ser-Lys-Arg-Lys-Leu-Nle-Glu-Ile-Ile-NH₂, wherein Y₁ is an acyl group having not more than 15 carbon atoms or is radioiodinated tyrosine, and wherein a cyclizing bond may exist between the side chains of Glu in the 31-position and Lys in the 34-position.